CYB5R3 gene

cytochrome b5 reductase 3

Normal Function

The *CYB5R3* gene provides instruction for making an enzyme called cytochrome b5 reductase 3. This enzyme is involved in transferring negatively charged particles called electrons from one molecule to another. Two versions (isoforms) of this enzyme are produced from the *CYB5R3* gene. The soluble isoform is present only in red blood cells, and the membrane-bound isoform is found in all other cell types.

Normal red blood cells contain molecules of iron-containing hemoglobin, which deliver oxygen to the body's tissues. The iron in hemoglobin is ferrous (Fe^{2+}), but it can spontaneously become ferric (Fe^{3+}). Hemoglobin that contains ferric iron is called methemoglobin, and it cannot deliver oxygen. The soluble isoform of cytochrome b5 reductase 3 changes ferric iron back to ferrous iron so hemoglobin can function. Normally, red blood cells contain less than 2 percent methemoglobin.

The membrane-bound isoform is embedded in the membranes of various cellular compartments and is widely used in the body. This isoform is necessary for many chemical reactions, including the breakdown and formation of fatty acids, the formation of cholesterol, and the breakdown of various molecules and drugs.

Health Conditions Related to Genetic Changes

autosomal recessive congenital methemoglobinemia

More than 65 mutations in the *CYB5R3* gene have been found to cause autosomal recessive congenital methemoglobinemia types I and II. Most of these *CYB5R3* gene mutations cause autosomal recessive congenital methemoglobinemia type I, which is characterized by a lack of oxygen in the body's tissues and bluish appearance of the skin, lips, and nails (cyanosis). The mutations that cause type I usually reduce enzyme activity or stability. As a result, the enzyme cannot efficiently change ferric iron to ferrous iron, leading to a 10 to 50 percent increase in methemoglobin within red blood cells. This increase in methemoglobin and corresponding decrease in normal hemoglobin reduces the amount of oxygen delivered to tissues. The altered enzyme activity affects only red blood cells because other cells can compensate for a decrease in enzyme activity, but red blood cells cannot.

The *CYB5R3* gene mutations that cause autosomal recessive congenital methemoglobinemia type II result in the more severe form of the two types. In addition to cyanosis, people with this form have neurological problems. The

mutations that cause type II typically result in a complete loss of enzyme activity. Cells cannot compensate for a complete loss of cytochrome b5 reductase 3, which results in a 10 to 70 percent increase in methemoglobin within red blood cells. This increase in methemoglobin and corresponding decrease in normal hemoglobin leads to cyanosis. The lack of enzyme activity in other cells leads to the neurological features associated with type II. Researchers suspect that the neurological problems are caused by impaired fatty acid and cholesterol formation, which reduces the production of a fatty substance called myelin. Myelin insulates nerve cells and promotes the rapid transmission of nerve impulses. This reduced ability to form myelin (hypomyelination) leads to a loss of nerve cells, particularly in the brain. The loss of these cells likely contributes to the encephalopathy and movement disorders characteristic of autosomal recessive congenital methemoglobinemia type II.

other disorders

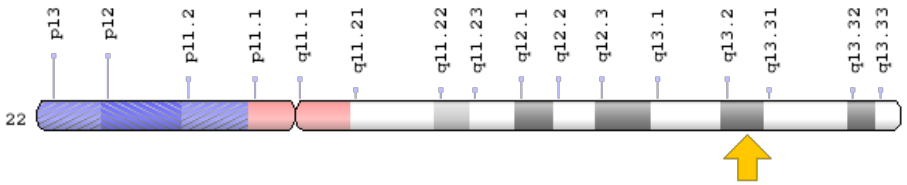
A normal variant (polymorphism) in the *CYB5R3* gene has been associated with low methemoglobin levels in infants who were born prematurely and treated with nitric oxide to prevent chronic lung disease. The lungs of premature infants are often underdeveloped and need support after birth. Nitric oxide widens the blood vessels of the lungs, allowing for more oxygen to get to the blood flowing through the vessels of the lungs. However, nitric oxide attaches (binds) to hemoglobin in red blood cells, which converts the hemoglobin into methemoglobin. If too much nitric oxide is administered to premature infants, more hemoglobin is turned into methemoglobin, and red blood cells cannot carry enough oxygen to the body's cells and tissues. This complication is known as methemoglobin toxicity. The polymorphism associated with low methemoglobin levels replaces the DNA building block (nucleotide) guanine with the nucleotide adenine at a specific place in the *CYB5R3* gene (written as 9015G>A). As a result, cytochrome b5 reductase 3 activity is increased, leading to an increased ability to convert methemoglobin back to hemoglobin, a rise in oxygen delivery, and a reduced risk of methemoglobin toxicity.

Another polymorphism in the *CYB5R3* gene has been found to increase the risk of breast cancer in African American women who smoke cigarettes. Cigarette smoke contains chemicals that can cause errors in DNA. These errors prevent cells from controlling their own growth and division, which can lead to the formation of a cancerous tumor. Normally, the cytochrome b5 reductase 3 enzyme can break down these chemicals into nontoxic substances, specifically targeting chemicals that have been shown to be involved in breast cancer. However, women who have a specific *CYB5R3* gene polymorphism that changes the way the gene's instructions are used to make the protein (written as I1M+6C>T) have reduced enzyme activity. As a result, the chemicals from cigarette smoke are not broken down. They cause errors in DNA that allow cells to grow without control or order, leading to breast cancer. Studies show that the *CYB5R3* gene polymorphism associated with breast cancer occurs at a 90-fold higher rate in African-American women than in white women.

Chromosomal Location

Cytogenetic Location: 22q13.2, which is the long (q) arm of chromosome 22 at position 13.2

Molecular Location: base pairs 42,617,840 to 42,649,399 on chromosome 22 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- B5R
- DIA1
- diaphorase-1
- NADH-cytochrome b5 reductase 3
- NADH-diaphorase 1
- NB5R3_HUMAN

Additional Information & Resources

Educational Resources

- Madame Curie Bioscience Database: Simulation Study for Methemoglobin Reduction Pathways
  https://www.ncbi.nlm.nih.gov/books/NBK6563/#A74876

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28CYB5R3%5BTIAB%5D%29+OR+%28cytochrome+b5+reductase+3%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- CYTOCHROME b5 REDUCTASE 3
  http://omim.org/entry/613213

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_CYB5R3.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=CYB5R3%5Bgene%5D
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=2873
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/1727
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